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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/167,088	Applicant(s) FINKELMAN ET AL.	
	Examin r Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1,4-23 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-23 and 25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 5/20/02 in Paper No. 17 is acknowledged and has been entered. Applicant's Declaration also filed 5/20/02 in Paper No. 18 is acknowledged. Claims 2-3 have been canceled. Claims 1, 6-8, 20, 26, and 37-39 have been amended. Accordingly, claims 1, 4-23 and 25-42 are pending and under examination.

Claim Objections

2. Claim 4 is objected to for depending from a cancelled claim. Appropriate correction is required.

Rejections Withdrawn

3. The rejections of claims 2-3 under 35 U.S.C. 112 and 103 are now moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4-23, and 25-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step a) is indefinite in reciting, "capable of binding" because it fails to define a positive limitation in the claim. Perhaps, Applicant intends "binds to".

Claim 1, step d) is indefinite in reciting, "capable of binding" because it fails to define a positive limitation in the claim. Perhaps, Applicant intends "binds to".

Claim 1, steps d) and e) are vague and indefinite in failing to define specifically what element of the targeting moiety - target analyte conjugate the capture moiety binds. Perhaps, Applicant intends in step e), "to allow that capture moiety to bind to the targeting moiety - target analyte conjugate and form targeting moiety - target analyte - capture moiety complexes in the assay mixture". Alternatively, if Applicant intends that the capture moiety binds to the targeting moiety element of the conjugate, then such should be reflected in the claim.

Claim 1 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, it is unclear in step g) how detection of the "amount of bound targeting moiety - target analyte conjugate" is performed in the absence of a label.

Claim 1 step h) is confusing. Step h) appears to recite a correlation step but fails to distinctly define how each of the elements in the claim relate, etc. so as to be consistent with and satisfy the requirement of the preamble. Perhaps Applicant intends, "wherein the amount of bound targeting moiety - target analyte conjugate bound on the

capture moiety detected in step g) is indicative of the amount of secreted target analyte in the sample ... or provides a measure of the production of secreted target analyte in the sample" or a similar language. Please refer back to the preamble.

Claim 7 recites improper overlapping Markush groups. Perhaps, Applicant intends, "wherein the blood sample is selected from ... whole blood, serum, and plasma."

Claim 13 is indefinite in reciting, "which can be bound to" because it fails to define a positive limitation in the claim.

Claim 20 is indefinite in reciting, "capable of being bound by" because it fails to define a positive limitation in the claim. Further, it is unclear, in the context of the claims what is encompassed by the term "recognized".

Claim 25 lacks clear antecedent support in reciting, "the bound conjugate", as dependent from claims 1, 8, and 20.

Claim 26 is indefinite in reciting, "which label can then be bound to" because it fails to define a positive limitation in the claim.

Claim 31 lacks antecedent support in reciting, "the molecule".

Claim 31 is indefinite in reciting, "capable of binding" because it fails to define a positive limitation in the claim.

Claim 34, part a) is indefinite in reciting, "capable of forming" because it fails to define a positive limitation in the claim. Alternatively, claim 34 is redundant in reciting, "specific for the target analyte and capable of forming a conjugate with the target

analyte". Perhaps, Applicant intends, "specific for the target analyte to form a conjugate with the target analyte".

Claim 34, part b) is indefinite in failing to distinctly define what portion of the targeting moiety - target analyte conjugate the capture moiety binds to.

Claim 37 is vague and indefinite in reciting, "having first targeting moieties ... having second targeting moieties" in relation to claim 1 from which it depends because it is unclear how the "[more than one] other targeting moieties" relate to the targeting moiety and target analyte which form a conjugate recited in claim 1. Specifically, claim 1 from which claim 37 depends only recite "a targeting moiety".

Claim 37 is indefinite in reciting, "capable of detecting and capable of amplifying" because it fails to define a positive limitation in the claim.

Claim 37 lacks clear antecedent support in reciting, "bound antibody from the second container".

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4-23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not appear to provide any literal support for the recitation of "in excess of measurable quantities of target analyte" in step a). Applicant points to page 19, lines 5, 6, 11-12 and page 21, lines 7-13 for antecedent basis; however, there is no literal support for this limitation in question. Limitations in claims that lack literal support in the specification constitute new matter.

6. Claims 1, 4-23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for in vivo targeting, in vitro capturing, and measuring production of secreted cytokines in the blood, does not reasonably provide enablement for in vivo targeting, in vitro capturing, and measuring of any other secreted protein in the peripheral blood. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method for measuring in vivo production of secreted peptide or protein hormone as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow binding of the targeting moiety to the peptide or protein hormone; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of peptide or protein complexes in an assay detection method.

The state of the prior art- the prior art of record fails to disclose a method wherein targeting moiety is injected to bind any and all secreted peptide or protein hormone in vivo then reacted with a capture moiety in vitro, to detect the presence or amount of targeting moiety - target analyte complexes.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method will work in any and all secreted peptide or protein hormone that is produced in vivo in human and animals.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work for measuring secreted cytokines in a human or animal. However, the specification fails to provide guidance to enable the claimed method to work for any and all peptide or protein hormone that is secreted in human and animals.

The presence or absence of working examples- working examples are provided in the specification that show that the claimed method works for measuring production of secreted cytokines in a human or animal. There are no working examples that show

analogous results in any other secreted peptide or protein hormone produced in vivo which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method for measuring in vivo production of secreted peptide or protein hormone as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow binding of the targeting moiety to the peptide or protein hormone; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of peptide or protein complexes in an assay detection method.

While the specification at page 18, lines 8-20 and page 20-23 describes using anti-cytokine antibody (or cytokine binding molecules) as neutralizing targeting moiety for injection into human or animal to bind cytokine in vivo, thus, causing accumulation of in vivo cytokine-anti-cytokine antibody complexes, and then binding the complexes to polyclonal capture antibodies immobilized into solid phase for assay detection in vitro, nowhere in the specification describes any other neutralizing targeting moiety that binds any other peptide or protein hormone to cause accumulation of such complexes in vivo, then reacts the complexes with capture antibodies in vitro, for use in a detection method of the peptide or protein hormone. The specification does not establish a direct correlation between cytokines and other peptides or protein hormones, which would

lead the skilled artisan to say that if the claimed method works for measuring endogenous cytokine production, then it should work in all other endogenously produced peptides and protein hormones secreted in a human or animal, to enable the breadth of the claimed method. Further, all working examples exemplify measuring in vivo production of endogenous cytokine using the claimed method. Additionally, in page 12, lines 20-25 of the specification, Applicant defines that the antibody for use as a neutralizing targeting moiety is "prototypical". While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only enabled for measuring in vivo production of secreted cytokine as the target analyte.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable detection of in vivo production of any and all secreted peptides and protein hormones using the claimed invention, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work in any and all secreted peptides or protein hormones; 3) there is no proper guidance that shows that the method can be performed for measuring the amount of any and all endogenous peptides and protein hormones in the instant specification, 4) the nature of the invention is a method for measuring in vivo production of any and all secreted peptide or protein hormone as

target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow in vivo binding of the targeting moiety to the peptide or protein hormone; thus forming complexes therebetween and then reacting the complexes with a capture moiety in vitro, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that prior art of record fails to disclose a method applicable for measuring an amount of any and all secreted endogenous peptides or protein hormones in a human or animal, and lastly 7) the claims broadly recite a method for measuring in vivo production of secreted peptide or protein hormone as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow binding of the targeting moiety to the peptide or protein hormone; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of peptide or protein complexes in an assay detection method. As recited, the instant method will measure in vivo production of any and all secreted peptide or protein hormone, regardless of where or how they are produced.

Therefore, it is maintained that one of skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4-23 and 25-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Pouletty et al. (US 5,612,034).

Tamarkin et al. disclose a competitive solid phase immunoassay for measuring the concentration of in vivo produced or endogenous, i.e. normal or stimulated, cytokines in the blood and other body fluids such as saliva, nasal secretions, tears and sweat in humans and animals (see Summary). Specifically, Tamarkin et al. disclose using one site assay system that is preferably polyclonal antibody based. According to Tamarkin et al., even when cytokine is bound to another molecule such as a cytokine binding protein, there is another part of the cytokine molecule that is available for site recognition (see column 9, lines 9-16). Tamarkin et al. discloses incubating a blood sample in the presence of a labeled targeting moiety, i.e. labeled antibody, that specifically binds cytokine, thus forming a cytokine - anti-cytokine antibody complex (cytokine bound to the labeled antibody), then reacting the complex to a capture moiety, i.e. polyclonal capture antibody, which recognizes many epitopes on the cytokine molecule to specifically bind the labeled cytokine - anti-cytokine antibody complex (see column 9, lines 48-53 and column 10, lines 19-43). The capture antibody is adsorbed to a solid phase support or carrier prior to reaction with the labeled complexes, i.e. biotinylated IL-1 (column 10, lines 18-43). The immunoassay system uses various

labels for cytokine detection including enzyme labels, fluorescent labels, radioactive elements, or luminescent labels (see column 7, lines 13-20, column 11, line 13 to column 12, line 11). The amount of cytokine in the complex may also be labeled and detected by linking the antibody with other binding partners such as biotin and streptavidin conjugated to an enzyme, i.e. alkaline phosphatase, followed by the addition of a chromogenic substrate -nitrophenyl phosphate (see column 10, lines 47-63 and column 11, lines 13-28). Tamarkin et al. also disclose kits for measuring cytokine comprising labeled antibodies, capture antibodies, buffers, standards, labels, and solid support (see columns 13-14).

Tamarkin et al. differ from the instant invention in failing to teach injecting neutralizing targeting moiety to the human or animal in order to form targeting moiety: target analyte conjugates in the peripheral blood circulation then obtaining a blood sample to measure the amount of target analyte present in the sample.

Pouletty discloses injecting a targeting moiety (binding entity or binding proteins) such as immunoglobulins and soluble receptors, into the bloodstream of mammalian hosts for binding with target analytes (target entities) such as cytokines, interleukins, and growth factors (see columns 7-8). The targeting moiety is generally a small molecule that is haptenic, i.e. biotin, or a ligand for a naturally occurring receptor or a substrate for an enzyme (see column 3, line 60 to column 4, line 9). The targeting moiety is administered via injection intravenously (see column 4, lines 40-50). The target analytes include cytokines, interleukins, growth factors, and interferons (see column 7, line 47 to column 8, line 16). In essence, Pouletty discloses that the targeting

moiety specifically binds the target analyte in vivo so as to allow for "capture" of endogenously secreted target analyte.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Pouletty in injecting specific targeting moieties into peripheral blood circulation of a human patient for binding specifically with endogenous target analytes such as cytokines, into the method of Tamarkin wherein a blood sample of the patient is obtained in order to measure the amount of endogenously produced cytokines using competitive solid phase immunoassay because Tamarkin specifically has shown the difficulty in obtaining an accurate measurement of endogenously produced cytokines because of a masking effect by *binding proteins* in the blood, and by specifically targeting and "capturing" the secreted analyte in vivo by injecting antibodies specific for the target analyte such as taught by Pouletty, an accurate amount and measure of the endogenous target analyte is obtained using the method of Tamarkin because the analyte is captured using polyclonal antibodies that recognize other epitopes present in the target analyte, separate from that bound in vivo to the target moiety.

Response to Arguments

8. Applicant's arguments with respect to claims 1, 4-23, and 25-42 have been considered but are moot in view of the new grounds of rejection. Applicant's declaration under 37 CFR 1.132 supporting the arguments has also been considered and addressed as follows.

A) Applicant argues that Tamarkin fails to use immunometric sandwich assays using monoclonal antibodies in measuring the concentration of macromolecules in the sample.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immunometric sandwich assay using monoclonal antibodies) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Specifically, the recited claims do not distinctly define an immunometric assay, the capture moiety is recited as polyclonal antibody, and the capture moiety has not been recited as a monoclonal antibody in the rejected claims.

B) Applicant argues that Pouletty fails to suggest measuring analyte production over time or that an excess of targeting moiety would need to be used in order to measure the total quantity.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the feature upon which applicant relies (i.e., measuring analyte production over time) is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Inasfar as using excess quantities of targeting moiety

for injection, the definition of "excess quantities" in the context of targeting moiety in the claim is subjective and unclear as to the metes and bounds required by the recited claim and in comparison to the teaching of the prior art.

C) Applicant argues that the combination of Tamarkin and Pouletty fails to suggest the claimed invention. Applicant's declaration also individually distinguished between the cited prior art and the instant invention.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Tamarkin is relied upon for the teaching of measuring endogenous cytokine production by binding cytokine to a labeled antibody specific for cytokine and a polyclonal capture antibody that recognizes binding sites of the cytokine. Pouletty is relied upon for teaching injecting antibody into a human for binding with the target analyte, i.e. cytokine, so as to capture secreted cytokine produced in vivo. It, therefore, would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Pouletty in injecting specific targeting moieties into peripheral blood circulation of a human patient for binding specifically with endogenous target analytes such as cytokines, into the method of Tamarkin wherein a blood sample of the patient is obtained in order to measure the amount of endogenously produced cytokines using competitive solid phase immunoassay because Tamarkin

specifically has shown the difficulty in obtaining an accurate measurement of endogenously produced cytokines because of a masking effect by *binding proteins* in the blood, and by specifically targeting and "capturing" the secreted analyte in vivo by injecting antibodies specific for the target analyte such as taught by Pouletty, an accurate amount and measure of the endogenous target analyte is obtained using the method of Tamarkin because the analyte is captured using polyclonal antibodies that recognize other epitopes present in the target analyte, separate from that bound in vivo to the target moiety.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Friday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

8/19/02

Christopher L. Chin

CHRISTOPHER L. CHIN
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